REMARKS

Applicants thank the Examiner for entering their amendment accompanying the response after final dated 26 May 2004. Following entry of that amendment claims 1-42 were pending, and claims 43-66 were cancelled. Claims 1-42 are again presented without further amendments and accompany by new claims 67 – 70 for the Examiner's consideration.

Incorporation by Reference

Applicants have amended the specification to recite subject matter from US patent 5,240,958 that was originally incorporated by reference. Support for the incorporation by reference can be found at page 9, lines 9-12, and at page 23, lines 17-22. No new matter is added by this amendment.

Rejection under 35 U.S.C. § 112 ¶ 2.

Applicants thank the Examiner for indicating the amendment accompanying the after final submission dated May 26, 2004 overcomes the previously outstanding rejection under 35 U.S.C. § 112 ¶ 2.

Rejection under 35 U.S.C. § 103

Claims 1-42 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over US 5,767,153 and WO 97/41844 or US 5,763,621.

In the Office Action dated March 8, 2004 and in the Advisory Action dated June 22, 2004, the Examiner has maintained the instant rejections holding Applicants' arguments to be non-persuasive.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103, *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988), in which there must be

some suggestion or motivation to modify or combine references and there must be a reasonable expectation of success, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or motivation to make the claimed combination, and the reasonable expectation of success, must be found in the prior art, and not based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d at 493.

A. The rejection of claims 1-42 under 35 U.S.C. 103(a) as allegedly being unpatentable over US 5,767,153 in view of US 5,763,621.

The Examiner's position is apparently that the cited art teaches the motivation to substitute the compositions of the primary reference into the secondary references is found in the primary reference, and is premised on the assertion that both primary reference and the '621 patent teach batimastat compositions.[1] The Examiner also contends that the '621 patent teaches that matrix metalloproteinase (MMP) inhibitors, including batimastat (BB-94), are useful in the treatment of proliferative retinopathies, and depends on these assertions to support the rejection.[2]

Applicants respectfully submit that even if the alleged motivation to combine the references did exist, the combination of references fails to render the instant invention obvious.[3] Contrary to the Examiner's assertion, the combination of references fails to teach or fairly suggest claimed methods for at least the reason that the '621 patent fails to teach the treatment of retinal neovascularization by topical administration of the compounds recited in the claims to the eye. Moreover, nothing identified by the Examiner suggests the skilled artisan would expect the

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[1] Office Action dated March 8, 2004 at page 3.

[2] *Id.*

[3] The absence of a motivation to combine the references is discussed on page 24 at lines 1-22.

compounds set forth in the claims to cross the sclera and reach the retina, thus, there is no reasonable expectation of success or motivation to combine the references.

Applicants have pointed out that the '621 patent fails to teach the treatment of retinal neovascularization by topical administration of the compounds recited in the claims to the eye. The Examiner has asserted in response that the '621 patent teaches "topical ocular formulation[s] which contain batimastat angiostatic compounds."[4] This is not the case because, the compounds recited in the '621 patent require the pendant functionality denoted R_4 to be an optionally substituted cycloalkyl or cycloalkenyl group. Thus, the compounds of formula (I) recited in the '621 patent does not encompass the compounds recited in the claims.

The Examiner also has alleged that the '621 patent teaches "topical application to the eye of batimastat (col. 11, l. 46) for the treatment of proliferative retinopathies."[5] Applicants respectfully disagree. As the '621 patent does not teach the compounds recited in the claims for the reasons discussed above, it cannot teach topical ophthalmic compositions containing them. Moreover, nothing the Examiner has identified, suggests that the topical ophthalmic compositions listed at column 11 of the '621 patent are suggested for use in the treatment of retinal neovascularization, as opposed to other ocular disorders that do not require the MMP inhibitors of '621 to cross the sclera and reach the retina.

Nothing identified by the Examiner suggests the skilled artisan would expect that topical application of the compounds recited in the claims to the sclera is a suitable route of administration for the treatment of retinal neovascularization, or that the compounds set forth in

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[4] Advisory Action dated June 22, 2004 at page 3.

[5] Office Action dated March 8, 2004 at page 4.

the claimed methods would reach the retina when applied to the sclera. Instead, the patent recognizes differences in the bioavailability of MMP inhibitors such as batimastat and those compounds that it teaches.[6] In addition, because the compositions recited in '621 do not contain the MMP inhibitors recited in the claims, they cannot be used to establish the bioavailabilty of the compounds recited in the claimed methods to the retina when topically applied to the eye. Thus, the '621 patent can provide no reasonable expectation of success of carrying out the claimed methods.

Applicants have also previously argued that a skill artisan would recognize that there is no reasonable expectation of success in treating retinal neovascularization by topical ophthalmic application of therapeutics as indicated by the teachings of Geroski *et al.*[7] Applicants maintain that Geroski *et al.* teaches "[t]opically applied drugs may enter the eye by crossing the conjunctiva and then defusing through the sclera, but . . . this approach typically does not yield therapeutic drug levels in the posterior vitreous, retina or choroid."[8] In response to these arguments the Examiner points to two references, WO 96/03985 and Ricci *et al.*, which the Examiner contends teach "topical administration of drug is exemplified and posterior segments of he eye are demonstrated to respond." Applicants respectfully submit that neither timolol employed by Ricci *et al.* nor the calcium channel-blocking agents employed in WO 96/03985 are the compounds employed in the claimed methods. In addition, the Examiner has failed to indicate where these references teach the recited drugs reached the retina, as opposed to other tissues through which they might exert their influence. Thus, they fail to demonstrate there is a

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[6] Applicants note that the only passage of the '621 patent that discusses batimastat acknowledges its poor bioavailability upon oral administration. Column 3 lines 36-47.

[7] See the response dated May 25, 2004 at pages 17-18 discussing the teachings of Geroski *et al.*

reasonable expectation that the compounds recited in the claims will reach the retina when topically administered to the eye, and for the this reason they cannot support a *prima facie* case of obviousness. Applicants further submit that the Examiner recognizes there are differences in the compounds employed in the claimed methods and those employed by WO 96/03985 and Ricci *et al.*,[9] which further evidences that these documents do not support the Examiner's assertion of obviousness.

Applicants have previously argued that the '621 patent teaches away from the instant claims. In response to Applicant's arguments the Examiner has alleged that "omitting an exemplification of a generic teaching is not the same as a teaching away from the claims," and that the " '621 patent certainly does teach a topical ocular formulation which contain batimastat angiostatic compounds."[10] The Examiner further alleges that "MMP inhibitors are disclosed to be effective against angiogenisis" and that together these teachings are "surely at the very least a suggestion to topically apply the compounds" of the '621 patent to treat proliferative retinopathies.[11]

Applicants respectfully submit the Examiner is mistaken, and maintain that the '621 patent teaches away from the claimed methods. The Examiner admits that the '621 patent omits a generic teaching. Moreover, as discussed above, the '621 patent not only omits a generic teaching, it does not teach the compounds set forth in the claimed methods, and as such, it cannot

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Footnote continued from previous page
[8] Geroski *et al.* at page 961 (emphasis added).

[9] See the Advisory Action dated June 22, 2004 at page 4.

[10] See the Advisory Action dated June 22, 2004 at page 3

[11] *Id.*

teach topical ocular formulation which contain the relevant compounds or their topical administration to the eye.

It is respectfully submitted that the relevant inquiry to determine if a reference teaches away articulated by the Court of Appeals for the Federal Circuit states that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be . . . led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed.Cir.1999) (quoting from *In re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994)). The '621 patent teaches away from the use of the compounds set forth in the claimed methods by instructing the use of other compounds having a "particular advantage of . . . oral activity together with broad spectrum activity against the metalloproteinase enzymes, including good potency against stromelysin." Moreover, the '621 patent leads away from topical administration as a route of drug delivery and emphasizes oral administration. In this regard the '621 patent specifically describes the MMP inhibitors it teaches as advantageously having "water-solubility and oral bioavailability."[12] This contrasts with the compounds recited in the claims, which the Examiner characterizes as water insoluble. Taken together, the teachings of the '621 patent are the use of water soluble MMP inhibitors and administration by an oral route. As such, this would lead a skilled artisan in a direction divergent from the path that was taken by the Applicant-- topical administration of water insoluble compounds. Thus, the teachings of the '621 patent are a teaching away from the topical administration of the compounds recited in the claims to the eye for the treatment of retinal neovascularization.

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[12] US 5,763,621, column 10, line 58-59.

Applicants submit that there is no motivation to combine the references, both because the Examiner is mistaken regarding the underlying premise upon which the motivation to combine the references is based, and because there can be "no suggestion to combine . . . if a reference teaches away from its combination with another source." *In re Fine,* 837 F.2d at 1074.

The Examiner alleges that the motivation to combine the references is found in the '153 patent, and that "[t]he substitution of the compositions of batimastat and polycarbophil disclosed in US 5,767,153 for the batimastat compositions taught in the methods of WO 97/41844 or US 5,763,621 would have been obvious because. . . ." Applicants respectfully submit that whatever else the '621 patent teaches it does not teach batimastat or a composition containing batimastat. Moreover, as discussed above, the '621 patent distinguishes batimastat from the compounds it teaches in column 1, at lines 38-46. Thus, the premise that a batimastat containing composition from the '153 patent could be employed in place of the batimastat compositions of the '621 patent, which underlies the Examiner's rationale for combining the references, is in error and fails to support a combination of these references. Moreover, Applicants submit that there can be no motivation to combine the '621 reference with the '153 reference when the '621 reference teaches away from the combination as discussed above.[13]

In light of the above, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-42 under 35 U.S.C. § 103(a) over US 5,767,153 in view of US 5,763,621.

[13] See page 22, line 7, through page 23, line 20.

B. The rejection of claims 1-42 under 35 U.S.C. 103(a) as allegedly being unpatentable over US 5,767,153 in view of WO 97/41844.

The Examiner has maintained the position that the cited art teaches the motivation to substitute the compositions of the primary reference into the secondary references, and that the secondary reference teaches the treatment of retinopathies.[14] The Examiner contends "WO 97/41844 clearly teaches the administration of combinations of angiostatic compounds to prevent pathological neovascularization (abstract) such as diabetic retinopathy. Batimastat is one of the specific angiostatic agents to be administered. In Example 1, a topical composition for controlling ocular neovascularization is taught."[15]

Applicants respectfully submit that contrary to the Examiner's assertion, the combination of references fails to teach or fairly suggest the claimed methods for at least the reason that the '41844 application fails to teach the treatment of retinal neovascularization by topical administration of the compounds recited in the claims to the eye. Moreover, nothing in the references would suggest to the skilled artisan that the compounds set forth in the claims would cross the sclera and reach the retina. As such, there is no reasonable expectation of success or motivation to combine the references.

Whatever else the '41844 reference teaches, it neither teaches nor fairly suggests topical compositions for the treatment of retinal neovascularization. Example 1 relied upon by the Examiner fails to specifically address retinal neovascularization. The retina is not only on the contralateral side of the cornea and sclera from which a topical therapeutic is administered, but

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[14] Office Action dated March 8, 2004 at page 3.

[15] Office Action dated 22 Jun 2004 at page two (emphasis omitted).

also in the posterior segment of the eye. Moreover, Applicants respectfully submit that the aqueous formulation in Example 1 is directed to "[t]opical combination compositions indicated as useful for controlling ocular neovascularization" of tissues that do with not include treatment of the retina. That the '41844 application does not include the retina in those tissues intended to be treated by topical administration is evident from statements in the specification. The statements "[s]olutions, suspensions and other dosage forms adapted for topical application to the involved tissues"[16] and "[t]hus, for topical administration, these formulations are delivered to the disease site 1 to 6 times a day,"[17] both require application of the dosage forms to the "affected tissues" or "disease site." A surgical exposure of the retina or injection are just not equivalent to topical administration. In addition, the '41844 disclosure specifically discusses those uses for which its topical formulations are suitable, stating "[t]opical ophthalmic formulations are suitable for preventing glaucoma filtration bleb failure or scar formation associated with ophthalmic surgery,"[18] none of which requires that active ingredients reach the retina.

As discussed above with regard to the rejection of claims 1-42 over the combination of the '153 and '621 patents, the combination of the '153 and '41844 references provides no reasonable expectation of success in treating retinal neovascularization by topical ophthalmic application of the compounds recited in the claims. As indicated by the teachings of Geroski *et al.*, "[t]opically applied drugs may enter the eye by crossing the conjunctiva and then defusing

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[16] Specification of the '41844 application at page 21, line 23, to page 22, line 1 (emphasis added).

[17] Specification of the '41844 application at page 24, lines 16-17 (emphasis added).

[18] Specification of the '41844 application at page 24, lines 7-8.

through the sclera, but . . . this approach typically does not yield therapeutic drug levels in the posterior vitreous, retina or choroid."[19] Thus, a skilled artisan would recognize there is no reasonable expectation of treating retinal neovascularization by topical ophthalmic application of the compounds recited in the claims. Also, as discussed above, neither the WO 96/03985 application nor the Ricci *et al.* reference that the Examiner relies upon support her position because they do not teach the compounds recited in the claims, and thus they cannot provide a reasonable expectation of success in delivering those compounds to the retina by topical ophthalmic application.

Although the Examiner has maintained the rejection of claims 1-42 over Applicants previous arguments, contending "capable of delivering" is directed to an inherent capacity of the composition recited in the claims,[20] the Examiner has previously stated that "it is assumed that the inference is that the medicament [taught by the '41844 reference] is expected to reach the retina in the absence of evidence to the contrary."[21] Applicants respectfully submit the Examiner bears an affirmative burden to establish a *prima facie* case of obviousness and that both the suggestion or motivation to make the claimed combination, and the reasonable expectation of success, must be found in the prior art, and not based on the Applicants' disclosure. *In re Fine*, 837 F.2d at 1074; *In re Vaeck*, 947 F.2d 493.

Applicants submit a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of the rejection and solicit a Notice of

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[19] Geroski *et al.* at page 961.

[20] Advisory action dated June 22, 2004 at 2.

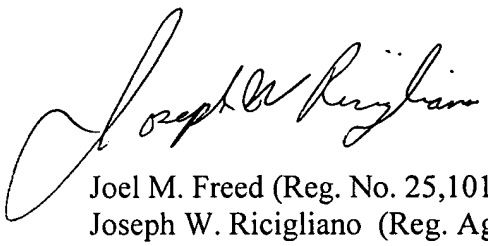
[21] Office Action dated March 8, 2004 at page 4 (emphasis added).

Allowance at the earliest possible time for the reasons recited above, and for the reasons of record in Applicants' previous responses.

CONCLUSION

In view of the foregoing Applicants believe the application is in condition for allowance and solicit a Notice of Allowance indicating such at the earliest possible time. The Examiner is encouraged to contact the undersigned should any additional information be necessary.

Respectfully submitted,



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